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# Psychosocial Group Intervention and the Rate of Decline of Immunological Parameters in Asymptomatic HIV-Infected Homosexual Men

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**Abstract**

The aim of the study was to determine changes in the rate of decline of immunological parameters after psychosocial group intervention. Subjects were 26 asymptomatic HIV-infected homosexual men who participated in a cognitive-behavioral group therapy (CBT; n = 14), or an experiential group therapy program (ET; n = 12), both of 15 weeks duration. The outcome measures were changes in the decline of CD4 cell counts, and T cell proliferative responses to anti-CD3 monoclonal antibodies from preintervention to 24 months postintervention. No differences in the rate of decline of CD4 cells or T cell responses between the CBT and ET condition were found, and there were no significant changes in CD4 cell count from pre- to postintervention. However, those subjects who showed larger decreases in distress showed a smaller decline in CD4 cell counts. While the rate of decline in T cell responses was significantly less after both interventions, a similar positive change in T cell responses was found in a comparison group of 149 HIV-infected men with similar demographic, psychosocial and immunological characteristics who did not participate in one of the interventions. We conclude that the psychosocial intervention programs tested here did not cause changes in CD4 cell decline or T cell responses and that decreases in distress were related to increases in CD4 cell counts.

**Key Words**
HIV infection
Psychotherapy
Immunology
Homosexual
Cognitive-behavioral
Experiential
Psychoneuroimmunology

## Introduction

After infection with human immunodeficiency virus type I (further abbreviated as HIV), the period until the development of acquired immunodeficiency syndrome (AIDS) varies considerably among individuals [1]. It is hypothesized that some of the variation is due to psychosocial factors, although several studies have yielded contradic-

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tory results [2]. These psychosocial factors may include stressful life events, psychological distress, coping styles and social support. In the event that psychosocial factors have an influence, psychosocial interventions may slow down the rate of progression and enhance the effectiveness of medical treatments.

Previous studies in healthy individuals [3] and cancer patients [4] have provided some evidence for an effect of psychosocial interventions on immunological parameters. Until now, however, only a few studies have been published on the immunological effects of behavioral interventions with HIV-infected people [5–7]. In one study, 47 healthy gay men were randomly assigned to a 10-week cognitive-behavioral stress management program or to an assessment-only control group [6]. Five weeks after entering the study, the men were notified of their HIV antibody serostatus. Two weeks later, the seropositive intervention subjects showed significant increases in CD4 and natural killer (NK) cell counts after serostatus notification, whereas the control group showed decreases. These findings may be important, because the number of CD4 cells is associated with progression of HIV infection and the onset of AIDS [1, 8, 9], while NK cells are involved in protection against tumors and viral infections [10]. Interestingly, the frequency with which relaxation was practiced at home during the intervention period was positively correlated with postintervention CD4 and NK cell counts, suggesting the possible importance of individual differences in treatment adherence [6]. However, the brief time frame of this study did not allow the investigators to address the effects of such interventions on the longer-term declines in immunological parameters that characterize the HIV spectrum of disease [1].

In contrast to these positive findings, another study found that an 8-week stress management program with HIV-infected men did not produce changes in immunological parameters, including CD4 cell counts, when compared with a waiting list control condition [5]. However, this intervention did not modulate distress levels either.

In the psychosocial intervention studies with HIV-infected individuals conducted to date, few immunological measurements have been tracked, and follow-up measurements have not been systematically obtained. The rate of decline of immunologic parameters may be of more prognostic relevance than single baseline measures. Therefore, no conclusions can be drawn with respect to the long-term potential health effects of such interventions. We tried to overcome these limitations by assessing changes in the rate of decline of immunological parameters after psychosocial intervention over a 2-year period. Immunological parameters were collected in the context of a natural history study at 3-month intervals beginning after testing HIV seropositive. This study was part of another study that investigated the psychosocial effects of cognitive-behavioral group therapy (CBT) and experiential group therapy (ET) [11]. In this previous study, it was shown that these interventions had equally beneficial effects on psychological distress as compared to a waiting list control group. Here we present the immunological findings, concerning changes in the rate of decline of immunological parameters after the psychosocial interventions.

## Methods

*Subjects*

All study subjects were recruited from a natural history study conducted at the Municipal Health Service of Amsterdam, The Netherlands, which began in 1984 [12, 13]. Thirty-nine subjects out of a group of 188 HIV-seropositive homosexual men followed in the natural history study (20.7%) agreed to participate in one

of the psychosocial interventions, and were randomly assigned to either a CBT or ET program. These men were all in CDC stage II or III (i.e., asymptomatic or having lymphadenopathy only [14]), and did not use antiretroviral medication at the time they were invited into the present study. Subjects were seen every 3 months for a physical examination, an interview regarding their medical status, and the collection of blood samples for immunological testing.

The 149 men who did not participate in one of the psychosocial interventions, but who fulfilled the inclusion criteria, were used as a natural history comparison group. Because the groups were self-selected, the comparison group was not a true control group. However, using the immunological data of this comparison group was thought to be of value in interpreting possible immunological changes observed after psychosocial intervention.

*Psychosocial Interventions*

Both the CBT and the ET program consisted of seventeen 2.5-hour sessions over 15 weeks. Details of these programs have been described earlier [11]. In short, it was found that both interventions showed significant effects on psychological distress [Profile of Mood States [(POMS); ref 15, 16], depressive symptoms [Beck Depression Inventory (BDI); ref. 17, 18] and psychiatric symptoms [General Health Questionnaire (GHQ); ref. 19, 20], as compared to a 4-month waiting list control group. However, no significant effects were found on coping styles (seeking social support, depressive reaction pattern, positive interpretation, problem-focused coping and denial), social-support satisfaction and emotional expression. There were no statistically significant differences between the CBT and ET program in their effects on the psychosocial measures mentioned above.

*Dropouts*

Although 39 men agreed to join the intervention study, 5 dropped out of the study before the start of the intervention due to practical reasons. During therapy, 3 men dropped out from the CBT and 5 from the ET groups. Reasons for dropping out included moving to another area and not feeling comfortable in the intervention group. The data of these dropouts were not included in the present analyses. Although the deletion of dropouts may bias the data, the results presented here do not change when dropouts are included. Thus, immunological effects of the intervention were analyzed for a total of 26 men (CBT: n = 14; ET: n = 12).

*Demographic Variables*

Information was obtained on age and known duration of HIV-seropositive status.

*Immunological Studies*

Immunological parameters were determined by the Netherlands Red Cross Blood Transfusion Service and were kindly provided for the present study.

CD4 cells and T cells responses were assessed at 3-month intervals from the time a subject entered into the natural history study and was determined to be HIV seropositive. These immunological outcome measures were chosen because they have been associated with clinical progression of HIV infection [1, 21].

*Determination of CD4 Cell Numbers*

Peripheral blood mononuclear cells were isolated from heparinized venous blood by density gradient centrifugation on a Ficoll-Paque gradient. Lymphocyte immunophenotyping was carried out by flow cytometry.

*T Cell Responses.* Lymphocyte proliferation was determined using the whole-blood lymphocyte culture technique described in detail elsewhere [22]. Briefly, heparinized venous blood was diluted 1:10 with Iscove's modified Dulbecco's medium supplemented with antibiotics and 2-mercaptoethanol ($5 \times 10^{-5}$ *M*). Triplicate cultures were performed in round-bottom microtiter plates containing 150 $mm^3$ diluted blood per well. The cells were stimulated with the monoclonal antibody CD3 CLB T3/4E [subclass IgE; final dilution, ascites $1:10^4$; ref. 23]. The proliferative response was measured after 4 days of culture by means of [$^3$H]thymidine incorporation added 24 h before harvesting. Reactivity was expressed as cpm per $10^3$ T cells.

*Psychological Assessment*

*Distress Changes in the Intervention Group.* We assessed the relationships between changes in affective state and changes in immunological parameters within the intervention groups. Distress was measured with validated Dutch adaptations of the POMS [15, 16] and the 21-item BDI [17, 18]. High POMS scores indicate high levels of mood disturbance for the 7 days preceding assessment ($\alpha$ of POMS: 0.89). Psychiatric symptoms were screened with a Dutch translation of the 30-item GHQ (GHQ-30; $\alpha = 0.94$), a widely used and well-validated instrument [19, 20]. For the purpose of this study, a psychological distress composite score was calculated by using a factor score derived from a factor analysis of the three distress scales (POMS, BDI, GHQ). This strategy was justified

by the high intercorrelations among the distress scales (r = 0.80–0.92).

*Baseline Psychological Characteristics in the Intervention and Comparison Group.* A screening battery including three items on depression, general anxiety level, and fear about getting AIDS (9-point scale) was administered at baseline to all 188 subjects, allowing us to characterize differences in participants versus nonparticipants (Cronbach's $\alpha = 0.81$). HIV-related coping behavior was also assessed at baseline by 10 items selected from a Dutch version of part of the situational version of the COPE, originally developed by Carver et al. [24]. The items were selected from two scales, measuring active coping (5 items; Cronbach's $\alpha = 0.64$) and seeking social support (5 items; Cronbach's $\alpha = 0.79$). No differences were found among the subjects in the intervention versus the natural history comparison group with respect to baseline affective state and HIV-related coping behavior ($p > 0.10$ for all measures).

*Procedures*

Psychological data collected immediately before and 6 months after the intervention were used for calculating the associations between changes in distress and changes in immunological parameters. The intervention started in early 1991. The immunological data collected through April 1993 were used for the present study.

*Statistical Analysis*

To evaluate changes in the decline of immunological parameters, we used the summary statistic method for analyzing laboratory marker changes in AIDS clinical trials [25].

Specifically, rate of change in immunological parameters was operationalized by calculating the slopes of the least-squares regression lines fit through each subject's immunological data collected at 3-month intervals during both the preintervention period (beginning at the time a subject was tested HIV seropositive in the natural history study), and continuing over a 24-month postintervention period.

Only subjects who had 3 or more data points during each of the pre- and postintervention periods were included in the analyses, as meaningful rates of change could not be calculated in subjects who had only 2 data points for a given period. No subjects in the intervention group and only 10 subjects in the comparison group were excluded from the analyses on these criteria. Ten subjects in the intervention group and 49 subjects in the comparison group started to use zidovudine (AZT) during the follow-up period ($\chi^2$, $p >$ 0.4). These subjects were *not* excluded from the analyses. The mean number of times that subjects had their CD4 counts and T cell responses recorded in the pre- and postintervention periods is described in the results.

The within-group changes in the slopes of the immunological parameters were analyzed using Wilcoxon matched-pairs signed-rank tests. Associations between changes in distress (from preintervention to 6-month follow-up) and changes in the decline of immunological parameters from the preintervention period compared to the postintervention period (until 24 months follow-up) were calculated using Spearman rank-order correlations. The slopes of the intervention and comparison group were compared using Mann-Whitney tests.

## Results

*Demographic, Psychological, and Immunological Characteristics at Baseline*

The demographic, psychological and immunological characteristics at baseline are reported in table 1. There were no differences in demographic, psychological and immunological variables assessed between the subjects in the intervention and comparison groups ($p > 0.10$ for all parameters). There were also no differences in demographic, psychological and immunological variables between the subjects undergoing CBT or ET intervention [11].

*Differences between the CBT, ET and Comparison Group in Rates of Decline of Immunological Parameters*

There were no significant differences in rates of decline of CD4 cells and T cell responses between the CBT and ET condition (table 2). Therefore, and because both interventions showed equal effects on distress, coping, social support and emotional expression [11], factors that might contribute to, or mediate immune changes [26], we combined the subjects assigned to the two intervention

**Table 1.** Demographic, psychological and immunological characteristics at baseline

| | Intervention group | Comparison group |
|---|---|---|
| Age, years | 40.4 (range 26–60) | 38.4 (range 21–61) |
| Known duration of seropositive status, years | 5 (range 1–7) | 4.6 (range 1–6) |
| Distress score | 3.7 (1.7) | 3.8 (1.9) |
| Seeking social support | 2.3 (0.8) | 2.1 (0.8) |
| Active coping | 3.2 (2.2) | 2.6 (2) |
| CD4 cells/mm$^3$ | 390 (200) | 469 (241) |
| T cell reactivity to anti-CD3 mAb per 1,000 CD3 cells, cpm | 127 (162) | 102 (115) |

Unless indicated otherwise, values in parentheses are SDs.

**Table 2.** Median of slopes of immunological parameters for subjects in the intervention groups (n = 26) versus those in the comparison group (n = 139)

| | Slope from first HIV-positive visit to intervention start | Slope from beginning of intervention to 24 months follow-up |
|---|---|---|
| *Slope of CD4 cell counts*[a] | | |
| Comparison group | −4.5 (−8.3 to −2.1; 16) | −4.6 (−9.2 to −1.3; 9) |
| Intervention group | −4.7 (−9.8 to −1.4; 18) | −3.4 (−6.6 to −0.3; 10) |
| *Slope of T cell response after stimulation with CD3 monoclonal antibody*[b] | | |
| Comparison group | −1.5 (−3.5 to 0.2; 10) | 1.8 (0.3 to 4.6; 9) |
| Intervention group | −1.7 (−3.8 to −0.3; 12) | 1.1 (−0.5 to 4.9; 10) |

The values in parentheses indicate first the range between the 25th and 75th percentiles, followed by the mean number of immunological tests on which the calculation of the slope was based.

[a] Slope: change in CD4 cells/mm$^3$/month.

[b] Slope: change in counts/min/1,000 T cells/month.

conditions for further analyses. There were also no differences in decline of the immunological parameters between the total intervention group (CBT + ET; n = 26) and the comparison group (n = 139) during 24-month follow-up after the intervention (Mann-Whitney tests, p levels >0.20).

*Within-Subject Changes in Rates of Decline of Immunological Parameters*

The rate of decline of CD4 cells did not change from the pre- to the postintervention period within the intervention (CBT + ET) or the comparison group (table 2). The slopes of T cell responses reversed during the 24-month postintervention period as compared to the

preintervention period, within both the intervention (CBT + ET) and the comparison group (Wilcoxon matched-pairs signed-rank tests, $p < 0.002$ for both comparisons).

*Distress-Immune Change Score Correlations*

Changes in psychological distress from preintervention to 6-month follow-up within the intervention group (CBT + ET) were significantly correlated with changes in the slope of the immunological parameters from preintervention to 24 months follow-up: $r = -0.39$, $p < 0.03$. This finding suggested that to some extent men with the largest reduction in psychological distress showed a smaller decline in CD4 cells in the postintervention period. However, there was no significant correlation between changes in psychological distress and the changes in the slope of the T cell responses over these periods ($p > 0.40$).

## Discussion

We found no changes in the rate of decline of CD4 cells in HIV-infected homosexual men after participation in a 15-week CBT or ET intervention of equal duration. However, the men with the largest reduction in psychological distress in both intervention conditions showed a smaller decline in CD4 cells.

There were no differences in the rate of decline of CD4 cells and decline of T cell responses to anti-CD3 monoclonal antibodies between subjects participating in one of the intervention programs as compared to a group of subjects who did not want to participate. Several problems remain, however, in the interpretation of these findings.

The design of this study precludes a true comparison between the intervention and comparison group because the comparison group was 'self-selected' and not randomly assigned. We do not know the reasons why the subjects in the comparison group decided not to participate in the psychosocial intervention programs. Although we did not find statistically significant differences between the intervention and comparison group in a number of demographic, psychosocial and immunological variables at baseline, it may be that the groups varied with respect to other characteristics. For instance, the subjects in the comparison group could have been less motivated to participate, having fewer difficulties in adjusting to HIV infection, because they may have been participating in other group support programs, or they may have had a more satisfactory social network.

We did not find changes in the decline of the immunological parameters after the group interventions. One reason for not finding an immunological change may be the lack of power due to a relatively small sample size. Another reason may be that the follow-up period was too short. Although we followed the subjects in the present study over a 2-year period, this may not have been long enough to detect a significant change. Burack et al. [27] found a predictive effect of depression on CD4 cell decline over a 6-year period.

In addition, it may be there were no immunological changes because there were also no significant changes in the subjects' coping styles, social support satisfaction and emotional expression [11]. As stated above, these factors might contribute to, or mediate immunological changes [26]. Finally, it may be that psychosocial group intervention does not change these specific immunological parameters in HIV-infected individuals, as was also found by Coates et al. [5] in their study using an 8-week intervention program.

The mean known duration of HIV-seropositive status in the intervention group was 5 years. It may be that HIV-infected individuals with a shorter known duration of HIV-sero-

positive status, and consequently more preserved immune functioning, are better candidates for testing the immunological effects of a psychosocial intervention, as was shown by Antoni et al. [6]. Although highly speculative, it may be that in HIV-infected individuals, immunological parameters such as T cell responses become refractory to psychosocial interventions over time, via muted reactivity to neuroendocrine changes following distress reductions after psychological interventions [28].

Within both the intervention and the comparison group we did find a significantly lower rate of decline of T cell responses during the 24-month postintervention period as compared to the preintervention period. This is probably due to a floor effect, because their proliferative responses were already at 50% of the level of non-HIV-infected controls at the beginning of the intervention period [M. Roos, Department of Immunology and Virology, CLB, Amsterdam, The Netherlands, pers. commun.]. Therefore, this finding is unlikely to reflect an actual improvement of T cell functioning.

The correlation between changes in CD4 counts and changes in distress might be explained in several ways. It may be that the men who showed a decrease in distress did so because they knew – based on the communications from their physicians – that they had stabilizing CD4 counts during the intervention and psychological follow-up. Alternatively, it may be that the reduction of distress during the intervention and follow-up period influenced the stabilization of the CD4 cell decline through psychoneuroimmunological mechanisms [27–29]. The absence of a correlation between changes in distress and changes in the slopes of T cell responses to anti-CD3 monoclonal antibody stimulation, however, does not support this last hypothesis.

A study using a randomized experimental design and a larger number of participants is needed to address some of the above-mentioned problems. In such a randomized study, not only should immunological effects be investigated, but also long-term clinical effects. In the event that certain psychosocial interventions are demonstrated to have biomedical as well as psychosocial effects, these treatments could be offered as an adjuvant treatment for HIV-infected homosexual men and possibly for other HIV-infected persons as well.


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